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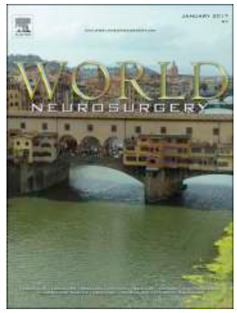

Bilaterally fixed and dilated pupils are not the kiss of death in patients with transtentorial herniation: a single surgeon's experience

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Bilaterally fixed and dilated pupils are not the kiss of death in patients with transtentorial herniation: a single surgeon's experience

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ABSTRACT

Introduction: Bilaterally fixed and dilated pupils in the setting of transtentorial herniation have traditionally been considered a sign of futility. Such patients are often denied life-saving surgery, based on the premise that meaningful functional recovery would be extremely unlikely. We sought to determine the survival and functional outcome in a cohort of patients who underwent aggressive medical and surgical management.

Methods: Retrospective chart review of all patients managed by a single surgeon over a 42-month period. Functional outcome was determined using modified Rankin Scale (mRS). Outcome was classified as: good (mRS 0-3), acceptable (mRS 4), or poor (mRS 5-6).

Results: Seven men and 2 women with mean age 36 years (range 16-66) were included. Etiology was: stroke in 4 patients, traumatic brain injury in 4, malignant cerebral edema in 1. Preoperative Glasgow coma score ranged from 3 to 7 and midline shift from 7 to 16 mm. All patients received emergency osmotic therapy before decompressive surgery. Time to surgery (from pupillary changes) was under 150 minutes for all patients (median 94, range 50-148). At 3 months, 5 patients (55.6%) had recovered, achieving a good (n=3) or acceptable (n=2) outcome. Four failed to recover and ultimately died because of their injury.

Conclusion: In well-selected patients with transtentorial herniation and bilaterally fixed and dilated pupils, aggressive and timely medical and surgical management may lead to substantial rates of survival and favorable functional outcome. Preconceived notions of a universally grim prognosis in such patients can lead to self-fulfilling prophecies.

Keywords: cerebral edema, craniotomy, craniectomy, non-reactive mydriasis, stroke, transtentorial herniation, traumatic brain injury.

INTRODUCTION

Non-reactive mydriasis in the setting of stroke or head trauma generally indicates transtentorial brain herniation secondary to mass effect from a space-occupying lesion, thus necessitating emergency medical and surgical management.[1] However, in contrast to patients with unilateral pupillary abnormalities, those with bilaterally fixed and dilated pupils are seldom managed aggressively, given a common perception of medical futility and the expectation of a universally poor outcome in this population.[2–16] In fact, multiple observational studies have consistently shown that bilateral non-reactive mydriasis is a reliable negative prognosticator in those patients, associated with high rates of mortality and poor functional outcome among survivors.[2,3,17–21]

However, in the absence of a randomized controlled trial, which would be challenging to conduct in light of ethical considerations, preconceived notions of an inevitably grim prognosis may be rooted in self-fulfilling prophecies rather than objective outcome data. In fact, overly pessimistic views among neurosurgeons could further help perpetuate such self-fulfilling prophecies by denying patients potentially life-saving decompressive surgery. Thus, challenging traditional beliefs, we postulate here, based on our own clinical experience, that a satisfactory functional outcome can often be achieved among survivors, provided aggressive medical and surgical treatment is administered without delay. For this purpose, we sought to retrospectively review our experience managing patients with transtentorial brain herniation and bilaterally fixed and dilated pupils at our stroke and trauma center.

MATERIALS AND METHODS

All patients who, between January 2018 and April 2021, underwent emergency decompressive surgery (i.e. craniotomy or craniectomy) by the senior author (R.R.) for transtentorial brain herniation with bilaterally fixed and dilated pupils, were included in this study. All patients were treated at a single stroke and trauma center and were identified from a prospectively maintained procedural database. Charts were retrospectively reviewed and clinical, radiologic, operative, and outcome data were recorded. The presence of bilaterally fixed and dilated pupils, defined as 5 mm or larger, was confirmed by reviewing emergency room (ER) provider notes and the surgeon's detailed operative report. Similarly, the presence of a space-occupying lesion and transtentorial brain herniation was confirmed by reviewing preoperative head CT images as well as the operative report. Patients with unilateral non-reactive mydriasis were excluded from the study. For each patient, the following data were collected: demographics, underlying etiology, clinical exam at presentation (including neurologic and pupillary exam performed with the patient off sedation), clinical exam at time of decompression, findings of head CT (including extent of midline shift), findings of cerebrovascular imaging (when available), use of osmotic therapy (including name and dose of osmotic agent), time to surgical decompression (from onset of bilateral non-reactive mydriasis), pupillary response after osmotic therapy, pupillary response after surgery, postoperative course, and functional outcome. Outcomes were assessed at 3, 6, and 12 months using the modified Rankin scale (mRS) and were grouped into the following categories: good (mRS 0-3), acceptable (mRS 4), or poor (mRS 5-6). Statistical analyses were performed using IBM SPSS Statistics for Windows version 27.0 (IBM Corp., Armonk, NY) and Prism version 9.2.0 (GraphPad Software, San Diego, CA). Univariate analyses were performed using Fisher's exact test for categorical variables and Mann-Whitney U test for numerical variables. p values less than 0.05 were considered statistically significant.

In our institution, patients with transtentorial brain herniation and pupillary changes are managed according to a well-defined protocol, which includes aggressive medical and surgical treatment and focuses on minimizing time delays. The slogan "time is brain" is frequently repeated and emphasized during operating room (OR) and ER huddles and meetings. This allows each member of the medical team to understand the importance of his/her own role in facilitating and expediting patient transfer to the OR for a timely surgical decompression. Unless therapeutic intervention is deemed futile, hemodynamically and respiratorily stable patients with transtentorial brain herniation and pupillary changes resulting from intracranial mass effect are immediately administered intravenous osmotic therapy, while the OR is alerted regarding the neurosurgical emergency. An OR is then immediately set up while the surgical team is en route. The target time for patient arrival in the OR is 60 minutes or less. When feasible, in well-selected cases, an external ventricular drain (EVD) is emergently placed at the bedside, thus allowing rapid partial decompression, prior to transfer to the OR for a more complete and definite decompression. In contrast to patients who are stable, hemodynamically or respiratorily unstable patients are first resuscitated in the ER or the intensive care unit (ICU) before being transferred to the OR for surgical decompression. Typical osmotic therapy at our institution includes: mannitol 0.5-1 g/kg + furosemide 20 mg +/- hypertonic saline bolus (3% or 23%). The decision to replace the bone flap (i.e. craniotomy vs. craniectomy) is usually made intraoperatively, at the end of decompression, based on the degree of brain relaxation achieved and the anticipated degree of postoperative cerebral edema (especially in younger patients with fuller brains). Postoperatively, patients are transferred to the ICU, where they are managed in standard fashion, including intracranial pressure (ICP) monitoring, via either an EVD or an ICP bolt monitor, when indicated. In accordance with standard guidelines, mean arterial pressure (MAP) is maintained above 85-90 mmHg and cerebral perfusion pressure (CPP) above 60 mmHg. In general, most patients with transtentorial brain herniation and pupillary abnormalities are offered aggressive treatment in our institution. There are a few exceptions, however, including: (1) patients with GCS 3 and bilaterally fixed and dilated pupils for a prolonged period of time (several hours or days), i.e. those with a near-brain death exam (defined as absence of motor response to pain with loss of upper brainstem reflexes, such as corneal and oculocephalic reflexes, but persistence of lower brainstem reflexes, such as cough and gag); (2) patients with bilaterally fixed and dilated pupils following cardiorespiratory arrest, especially those with anoxic brain injury; (3) patients who are very old, with pre-existing severe disability (e.g. prior brain injury), and/or limited life expectancy (e.g. terminal cancer); (4) patients who remain hemodynamically or respiratorily unstable despite maximal resuscitation. Whenever possible, especially in borderline surgical cases, the patient's healthcare proxy or next-of-kin is contacted by the surgeon, while en route to the OR, and his/her input solicited in the decision-making process.

RESULTS

During the study period, nine patients, 7 men and 2 women with a mean age of 36 years (range 16-66), underwent emergency decompressive surgery for transtentorial brain herniation with bilaterally fixed and dilated pupils (Tables 1 and 2). Etiologies of brain herniation included: spontaneous intracerebral hemorrhage (ICH) in 4 patients, traumatic brain injury (TBI) in 4, and malignant cerebral edema in 1. Spontaneous ICH was secondary to: aneurysm rupture in 1 patient, arteriovenous malformation rupture in 1, tumoral hemorrhage in 1, and hypertension in 1. In patients with TBI, the underlying mass lesion was: epidural hematoma in 2, traumatic ICH in 1, and subdural hematoma in 1. In the single patient with malignant cerebral edema, brain herniation was a direct complication of hemodialysis (severe dialysis disequilibrium syndrome), approximately one week following the resection of an insular glioma. The left cerebral hemisphere was primarily affected in 5 patients (55.6%), while the right hemisphere was involved in 4 (44.4%). Three patients (33.3%) were hemodynamically unstable at presentation, requiring aggressive resuscitation in the ED. None of the patients in this series, however, had bilateral non-reactive mydriasis at presentation. In fact, all 9 patients developed bilateral pupillary changes in the hospital, either while in the ER or following hospital admission. Nonetheless, 3 patients did initially present with a unilaterally fixed and dilated pupil, then blew the contralateral pupil shortly thereafter. Median Glasgow coma scale (GCS) score on admission was 11 (range 3-15), but had dropped to 3 (range 3-7) preoperatively. At the time of surgery, 7 patients (77.8%) had preserved corneal and gag reflexes and mean midline shift on CT was 9.8 mm (median 9, range 7-16).

All 9 patients received emergency intravenous osmotic therapy preoperatively, resulting in improved pupillary exam, i.e. reduction in size and/or improved response in at least one pupil, in 3 patients (33.3%). Time to skin incision (from bilateral pupillary changes) was under 150 minutes for all patients (mean 100, median 94, range 50-148). Bone flap was successfully replaced in 6 patients (66.7%), while 3 (33.3%) required a craniectomy. Postoperatively, pupillary response was improved in 6 patients (66.7%), including 3 who had responded to preoperative osmotic therapy. One patient (11.1%) died in the early postoperative period. Of the eight survivors, 6 (66.7%) exhibited gradual neurologic improvement, including 2 who were successfully extubated. Five patients were discharged to an acute rehabilitation facility, while 3 were transferred to long-term care. Median GCS score at discharge among survivors was 11 (range 3-15). Of 6 patients who had undergone tracheostomy and gastrostomy, 3 were eventually decannulated, while 3 died in the first 6 months following surgery. All 3 patients who had undergone a craniectomy ultimately received a cranioplasty.

Functional outcome data was available at 3, 6, and 12 months for all patients (Figure 1). At 3 months, 5 patients (55.6%) had achieved either good (n=2, 22.2%) or acceptable (n=3, 33.3%) outcomes. In contrast, 2 had died (22.2%) and 2 remained severely disabled (22.2%). Between 3 and 6 months, one patient with moderately severe disability (mRS 4) exhibited significant neurologic improvement, while 2 patients with severe disability (mRS 5) died. Thus, at 6 months, no patients were alive with severe disability. In contrast, at 6 and 12 months, all 5 survivors had achieved either good (n=3, 33.3%) or acceptable (n=2, 22.2%) outcomes.

One patient with initially excellent outcome (mRS 2) died approximately 5 months after surgery. This 18-year old patient, who initially presented with a massive spontaneous ICH of unclear etiology (a complete workup, including cerebral angiography and MRI, was completely negative), was readmitted a few months later with a new spontaneous ICH of the contralateral hemisphere. Although he had managed to survive and recover very well from the first ICH (mRS 2, ambulatory and functionally independent, free of infection), his second hospital admission was marked by a protracted and complicated course, including EVD infection leading to ventriculitis, meningitis, and sepsis, ultimately resulting in his death. A repeat etiologic workup, including cerebral angiography and MRI, was again obtained during that second admission and remained completely negative.

All 3 patients who exhibited improved pupillary response after osmotic therapy had good outcome. Similarly, of 6 patients who showed improved pupillary response after decompressive surgery, 4 (66.7%) had either good (n=3) or acceptable (n=1) outcome (Figure 2). However, on univariate analysis, none of those associations reached statistical significance. In contrast, younger age was the sole variable found to significantly predict a favorable (good or acceptable) outcome in this series (Table 3). Interestingly, in all 3 patients with good functional outcome (mRS 0-3), the dominant hemisphere was involved.

DISCUSSION

In this retrospective review of the experience of a single surgeon, we found that aggressive medical and surgical management of well-selected patients with intracranial mass lesions, transtentorial brain herniation, and bilaterally fixed and dilated pupils, can often lead to meaningful neurologic and functional recovery. Specifically, in this small series of 9 patients, 5 survivors had good or acceptable functional recovery (mRS 0-4), including 3 with only mild or moderate disability (mRS 0-3). More importantly, all 4 patients who failed to recover ultimately died in the first 6 months following surgery, leading to no instances of chronic severe disability or persistent vegetative state in this series. Those results seem to challenge the traditional belief that, in the setting of transtentorial herniation, the presence of bilaterally fixed and dilated pupils is the “kiss of death”, representing the point of no return, at which medical and surgical interventions become largely futile and neurologic damage irrecoverable.

It is likely that both judicious patient selection and the implementation of an aggressive, institution-wide management protocol for such patients may have contributed to the relatively favorable results in this series. For instance, very old patients, especially those with pre-existing severe disability and/or limited life expectancy were generally not offered life-saving decompressive surgery. Given that young age is associated with better neurologic recovery, such a selection strategy would be likely to increase the rate of favorable outcomes. Notwithstanding, age alone was never used as a standalone criterion (i.e., without consideration of functional status and medical/physiologic condition) to deny patients a life-saving decompressive surgery. Similarly, patients with near-brain death exams and those with bilaterally fixed and dilated pupils for prolonged periods of time, including those with anoxic brain injury, were not offered surgery. Moreover, patients had to be hemodynamically and respiratorily stable before undergoing decompressive surgery in the OR.

The importance of rapid relief of transtentorial brain herniation and brainstem compression in such cases cannot be overstated, even when such relief is temporary. For this reason, we always immediately administer intravenous osmotic therapy while preparations for OR transfer are underway. Occasionally, placement of an EVD at the bedside, prior to transfer to the OR, can also help provide temporary control of ICP and relief of brainstem compression. Such temporary relief is crucial in helping the brainstem survive prolonged periods of mechanical compression and impaired perfusion. In fact, in this series, all 3 patients who exhibited improvement in pupillary response following osmotic therapy ultimately had a favorable outcome. In contrast, all 4 patients who ultimately died had failed to respond to osmotic therapy. Although this association failed to reach statistical significance, exhibiting only a statistical trend, this small series was likely underpowered to detect such an association. To the best of our knowledge, the impact of preoperative pupillary response to osmotic therapy on functional outcome in this patient population has not been previously examined. Moreover, thanks to our aggressive management protocol, time to surgery in this series was under 150 minutes for all patients, substantially shorter than that reported in prior studies.[10,12,15,22] It is quite likely and quite intuitive that a shorter time to surgery may lead to higher rates of survival and functional recovery in this patient population.

In fact, previous literature on this topic has generally emphasized the poor prognosis of patients who develop bilaterally fixed and dilated pupils secondary to transtentorial brain herniation.[17–19] In reporting TBI outcomes, some authors have actually gone so far as to exclude patients with bilaterally fixed and dilated pupils from their data sets, referring to bilateral non-reactive mydriasis as a "fatal prognosis".[18,23] In a retrospective study of 245 TBI patients, Tien et al[12] documented a 100% mortality rate among patients with bilaterally fixed and dilated pupils and a GCS score of 3. In a similar study, Jamous et al[24] found that all 21 patients with bilaterally fixed and dilated pupils and GCS 3, including 5 who underwent emergency decompressive craniectomy, died within 30 days of trauma. In a study of 44 TBI patients who underwent decompressive craniectomy, Tian et al[25] observed a favorable functional outcome in only 9.1% of patients at 3 months, improving to 20.5% at 12 months. In a similar study of 40 TBI patients, Sakas et al[22] reported a 25% rate of good outcome or moderate disability 1 year after craniotomy. In a recent systematic review of the published literature, we uncovered an overall rate of survival of 33% and an overall rate of favorable functional outcome of 17% in this patient population.[26]

A common concern, when it comes to life-saving decompressive surgery in such patients with devastating injuries, is the potential to unnecessarily prolong life in a state of severe disability or persistent vegetative state.[24] However, in this study, all 4 patients who failed to recover after surgery ultimately died within the first 6 months, resulting in no patient surviving in a chronic state of severe disability or persistent vegetative state. In addition, functional improvement continued to occur among survivors in the first 12 months after surgery, with one patient progressing from moderately severe disability (mRS 4) to moderate disability (mRS 3). This observed improvement over time in functional outcome of TBI and stroke patients is in line with previous reports.[25] Although the classification of moderately severe disability (mRS 4) as an "acceptable" outcome may be subject to debate, we have previously shown that, notwithstanding their significant functional limitations, most survivors with moderately severe disability are generally happy to be alive and do not regret having had life-saving surgery.[27]

Our study has limitations. First and foremost, the small sample size limits our ability to draw firm conclusions. Second, the retrospective nature of the study renders our findings susceptible to inherent methodological biases, including a clear selection bias favoring younger and healthier patients, as well as those with a lesser degree of neurologic devastation. However, while such a selection bias can positively skew outcome data, the study's pragmatic design allows a more accurate representation of real-world neurosurgical experience. Real world representation is further strengthened by the inclusion of all etiologies of transtentorial brain herniation in this study, including TBI and stroke, while the majority of previous publications had focused, almost exclusively, on traumatic etiologies.

CONCLUSIONS

In well-selected patients with bilaterally fixed and dilated pupils secondary to intracranial mass effect and transtentorial brain herniation, aggressive medical and surgical management can result in substantial rates of survival with meaningful neurologic recovery. Timely administration of intravenous osmotic therapy and rapid transfer to the OR are key to achieving a favorable outcome. While large prospective studies are warranted to confirm these findings, including the prognostic value of pupillary response to osmotic therapy, such patients should not be denied life-saving decompressive surgery based on preconceived notions of futility in this patient population.

Disclosures: None

Conflict of interest: None

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FIGURE LEGENDS

Figure 1. Functional outcome

*One patient with excellent functional outcome (mRS 2) later died approximately 5 months after surgery, secondary to second, unrelated ICH in contralateral hemisphere (see text).

Figure 2. Pupil response to treatment and outcome.

*One patient with excellent functional outcome (mRS 2) later died approximately 5 months after surgery, secondary to second, unrelated ICH in contralateral hemisphere (see text).

Table 1. Baseline characteristics.

N	9
Age, mean ± SD (range)	36 ± 17 (16-66)
Male sex, n (%)	7 (77.8%)
GCS preoperative, median (range)	3 (3-7)
Brainstem reflexes intact, n (%)	7 (77.8%)
Midline shift (mm), mean ± SD (range)	10 ± 3 (7-16)
Pupil response to osmotic therapy, n (%)	3 (33.3%)
Time to surgery (min), mean ± SD (range)	100 ± 36 (50-148)
Pupil response to surgery, n (%)	6 (66.7%)
GCS at discharge, median (range)	11 (3-15)
mRS at 3 months, median (range)	4 (1-6)

GCS, Glasgow coma scale score; mRS, modified Rankin scale score; SD, Standard deviation

Table 2. Summary of cases

#	Age (y), Sex	Etiology	Preop GCS	Midline Shift (mm)	M/HS/FS Administered	Time to Surgery (min)	Side/Type of Surgery	Pupil Response After Surgery	Discharge Disposition	3-month mRS	12-month mRS
1	26, M	ICH (aneurysm)	3	9	+/-/+	80	R Craniotomy, Hematoma Evacuation, Aneurysm Excision	Reactive	Acute Rehabilitation	4	4
2	18, M	ICH (AVM)	3	11	+/+/+	144	L Craniotomy, Hematoma Evacuation, AVM resection	Reactive	Acute Rehabilitation	2	6*
3	36, M	SDH (trauma)	7	9	+/+/+	94	L Craniotomy, Hematoma Evacuation	Reactive	Acute Rehabilitation	1	1
4	27, M	EDH (trauma)	4	10	+/-/+	85	L Craniotomy, Hematoma Evacuation	Reactive	Acute Rehabilitation	4	4
5	33, F	DDS (malignant edema)	3	7	+/-/-	57	R Craniectomy	Non-reactive	Died	6	6
6	43, M	ICH (trauma)	3	10	-/+/-	148	R Craniotomy, Hematoma Evacuation	Non-reactive	Long-Term Care	5	6
7	55, M	ICH (hypertension)	3	8	+/+/+	132	L Craniectomy, Hematoma Evacuation	Non-reactive	Long-Term Care	6	6
8	66, F	ICH (tumor)	3	16	+/+/-	107	R Craniectomy, Hematoma Evacuation, Tumor Resection	Non-reactive	Long-Term Care	5	6
9	16, M	EDH (trauma)	3	8	+/-/+	50	L Craniotomy, Hematoma Evacuation	Reactive	Acute Rehabilitation	4	3

AVM, arteriovenous malformation; DC, decompressive craniotomy/craniectomy; DDS, dialysis disequilibrium syndrome; EDH, epidural hematoma; F, furosemide; GCS, Glasgow coma score; HS, hypertonic saline; ICH, intracerebral hemorrhage; ICU, Intensive care unit (ICU); L, left; M, mannitol; mRS, modified Rankin scale score; Preop, preoperative; R, right; SDH, subdural hematoma

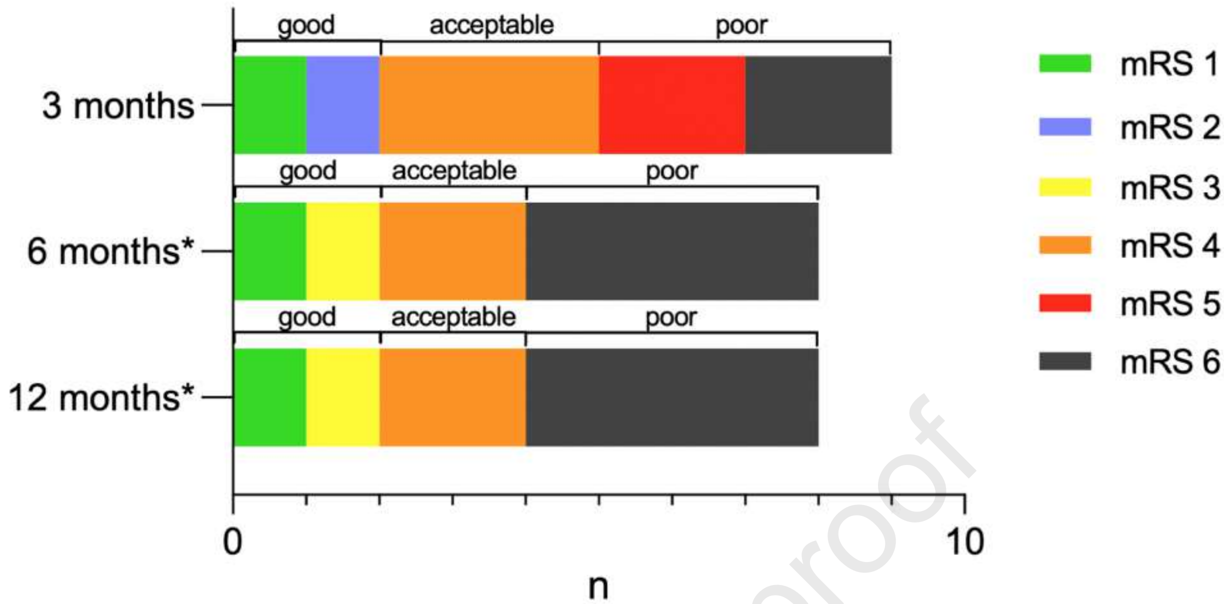
* Patient with excellent functional outcome (mRS 2) later died approximately 5 months after surgery, secondary to second, unrelated ICH in contralateral hemisphere (see text).

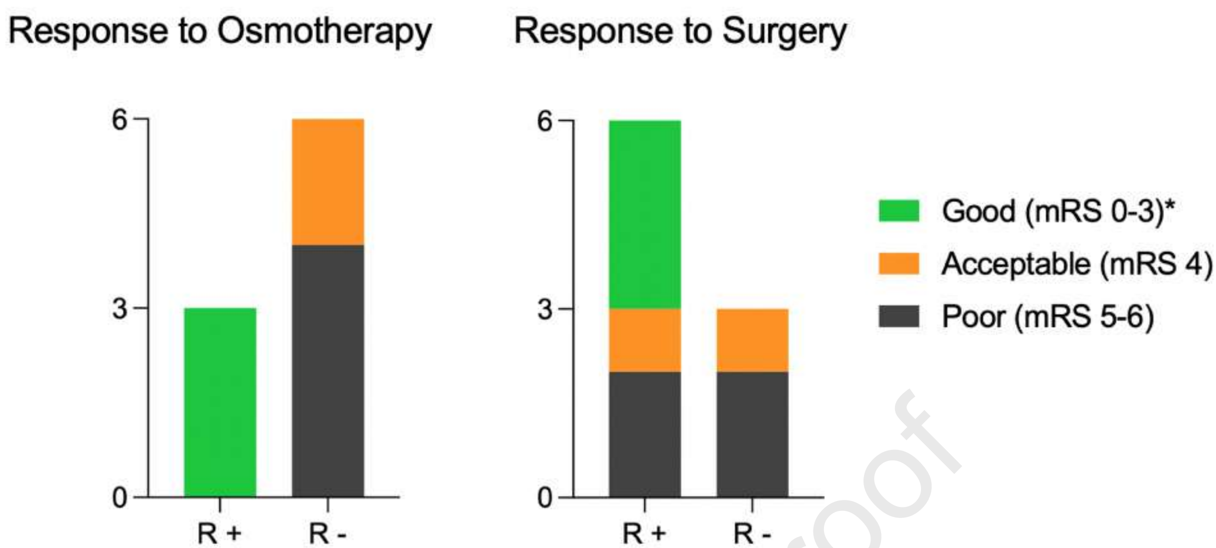
Table 3. Prognostic variables

	Good or Acceptable Outcome (mRS 0-4) *	Poor Outcome (mRS 5-6)	p
N	5	4	
Age, mean ± SD (range)	25 ± 8 (16-36)	49 ± 14 (33-66)	0.03
Male sex, n (%)	5 (100%)	2 (50%)	NS
GCS preoperative, median (range)	3 (3-6)	3 (3-3)	NS
Brainstem reflexes intact, n (%)	5 (100%)	2 (50%)	NS
Midline shift (mm), mean ± SD (range)	9 ± 1 (8-11)	10 ± 4 (7-1.6)	NS
Pupil response to osmotic therapy, n (%)	3 (60%)	0 (0%)	NS
Time to surgery (min), mean ± SD (range)	91 ± 34 (50-144)	111 ± 40 (57-148)	NS
Pupil response to surgery, n (%)	4 (80%)	2 (50%)	NS

GCS, Glasgow Coma Score; mRS, modified Rankin Scale; NS, not significant

*Analysis includes one patient with excellent functional outcome (mRS 2) later died approximately 5 months after surgery secondary to second, unrelated ICH in contralateral hemisphere (see text).


good
acceptable
poor
3 months
6 months*
12 months*
0
10
n
mRS 1
mRS 2
mRS 3
mRS 4
mRS 5
mRS 6


Response to Osmotherapy
Response to Surgery
6
3
0
R +
R -
Good (mRS 0-3)*
Acceptable (mRS 4)
Poor (mRS 5-6)

Decompressive craniectomy or craniotomy (DC)

Epidural hematoma (EDH)

Glasgow coma scale (GCS)

Glasgow outcome scale (GOS)

Intracerebral hemorrhage (ICH)

Subarachnoid hemorrhage (SAH)

Subdural hematoma (SDH)

Bilaterally fixed and dilated pupils (BFDP)

emergency room (ER)

external ventricular drain (EVD)

intensive care unit (ICU)

intracranial pressure (ICP)

traumatic brain injury (TBI)

Daniel Griepp: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing.

Aaron Miller: Conceptualization; Formal analysis; Investigation; Software; Supervision; Validation; Visualization; Writing - review & editing.

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